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(54) Small particle drug compositions for nasal administration

(57) A pharmaceutical composition for intranasal use comprises a plurality of microspheres which are adhesive to the nasal mucosa, and an active drug associated with each microsphere, at least 90 wt % of the microspheres having a diameter in the range 0.1 µm to 10 µm.

The microspheres may be of starch, gelatin, dextran, collagen, albumin or of the drug itself, which may be a peptide, such as insulin or calcitonin. The composition may additionally comprise an absorption enhancer, e.g. a surfactant. The composition may be administered in a gas stream.

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SMALL PARTICLE DRUG COMPOSITIONS

The present invention relates to drug compositions and more particularly to a small particle drug composition which provides for the uptake of active drug across the nasal mucosa.

There is a need to provide effective absorption of high molecular weight material such as proteins and peptides across biological membranes. Normally such molecules are not taken up by the body if administered to the gastrointestinal tract, to the buccal mucosa, to the rectal mucosa, the vaginal mucosa or if given as an intranasal system. Because peptide hormones such as insulin and calcitonin have a high molecular weight and are readily decomposed by proteolytic enzymes such as pepsin, aminopeptidases, trypsin and chymotrypsin, not enough is absorbed to display an effective pharmacological effect and accordingly they have been administered by parenteral injection.

However, since the administration by injection causes pain, various attempts have been made to develop alternative methods of administration.

Recent studies with the material insulin have demonstrated that the absorption of such a compound can be increased if it is given together with a so-called absorption enhancer, such as non-ionic surfactants and various bile salt derivatives. An increased permeability of membranes in the presence of these types of surfactant material is not unexpected, indeed the literature in the field of gastroenterology contains a wide range of such absorption promoters. (For a review see Davis _et al_ (editors), _Delivery Systems for Peptide Drugs_. Plenum Press, New York 1987.) However, such materials will probably not be acceptable for the chronic administration of pharmacological agents because of their irritant effects on membranes. This includes not only the non-ionic variety of surface active agents but also bile salts and bile salt derivatives (e.g. fusidic acid).

At the present time the nose is being proposed as an alternative route for the delivery of drugs that will act within the systemic circulation. Particular attention is being focused on nature-identical peptides or proteins, or analogues or fragments thereof, produced by recombinant DNA techniques. Other drugs that are being suggested are those that are poorly absorbed orally or are extensively metabolised either in the gastro-intestinal tract itself or are subject to first pass metabolism in the liver.

However, most polypeptide drugs show availability when administered intranasally.

The rapid clearance of nasal sprays from the nose can probably be considered to be a major factor in influencing loss of drugs from potential absorption surfaces. In addition, in the case of peptides and proteins, enzymatic degradation of the drug and molecular size may also have a role in giving low bioavailabilities.

Our earlier co-pending application WO88/09163 discloses intra-nasal microsphere formulations containing an enhancer and our earlier co-pending application WO89/0327 discloses intra-nasal microsphere formulations containing drugs of molecular weight below 6000 which do not require an enhancer. In both of these applications, the diameter of the microspheres is in the range 10 µm to 100 µm. EP 122 036 (Teijin Ltd.) discloses powdery formulations for nasal administration in which at least 90 wt % of the particles have an effective diameter ranging from 10 µm to 250 µm.

It is taught in the art that particles for nasal delivery should be of diameter greater than 10 µm. EP 122 036 states that in compositions for nasal administration in which more than 10 wt % of the particles are below 10

μm, more particles will go further into the lungs or escape from the nostrils. It is known to use particles of diameter less than 10 μm for delivery of drugs to the lungs. GB 1 381 872 and GB 1 520 248 (Fisons) describe powdery compositions of particles less than 10 μm which are administered by oral inhalation to the lungs.

It has now been found, surprisingly, that bioadhesive microspheres of diameter less than 10 μm can be used effectively and advantageously to deliver drugs to the nasal mucosa.

A first aspect of the invention therefore provides a drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and active drug associated with each microsphere, at least 90 wt % of the microspheres having a diameter of 0.1 μm or more but less than 10 μm. The term "bioadhesive" as used herein is defined as a substance which adheres to the nasal mucosa, preferably to a greater extent than microcrystalline cellulose. It is thought that such bioadhesive microspheres interact with the glycoproteins in the mucus and/or, the epithelial cells. The term "drug" is used to embrace any pharmacologically active agent, including hormones, polypeptides and vaccines or components thereof, for example isolated antigens or antigenic parts or mimics thereof.

For any particulate system consisting of a distribution of particle sizes, it is important to define exactly the way in which the diameter is measured. A powder system produced by milling or emulsification followed by suitable processing to yield microspheres (this includes both powders and bioadhesive microspheres) is expected to follow a so-called log normal distribution. Particle size measured by microscopic observation will give a number average distribution. This can be converted to a weight distribution (number-weight, mean diameter), using equations found in standard text books such as T. Allen, Particle Size Measurement, second edition, Chapman and Hall, 1974 and Caserett, L.J. in Toxicology, edited by Casarett, L.J. and Doull, J., Macmillan, New York, 1975, chapter 9.

In the latter, it is stated that the customary expression of particle size is in terms of the median size, either count or mass. For a log normally distributed powder conversion between a count median diameter (CMD) and a mass median diameter MMD is easily accomplished by a simple calculation where δg is the geometric standard deviation:-

$$\log M \text{ (Count)} = \log M' \text{ (Mass)} - 6.9 \log^2 \delta g$$

The weight distribution can be measured directly by screening or sieving or by sedimentation balance. Details are given in the book by Allen (see above).

For a spherical particle, size is uniquely defined and it is possible to talk about a mean diameter. However, with non-spherical particles it is necessary to consider an effective diameter as the size of a sphere that corresponds to the particle under the chosen conditions of measurement. The various options are discussed in the book by T. Allen, where derived diameters are determined by measuring a size dependent property of the particle and relating it to a linear dimension. Effective diameter has been defined by Teijin, so far as it applies to their nasal delivery system, in EP 23359. They refer to a diameter as determined by the opening sizes of sieves. For example, a powder having an effective particle diameter (d) of $37<d \leq 44$ passes through a sieve having an opening size of 44 microns but does not pass through a sieve having an opening size of 37 microns.

A vibratory sieve is used when the effective particle diameter of a powder is more than 37 microns, and a sonic sieve (Micro Hand Sifter SWM-2, a product of Tsutsui Rikagaku Kikai Co. Ltd.) is used when the

the present invention have a true mean weight diameter of less than the 10μm effective diameter of the Teijin particles. Preferably 90 wt% of the microspheres are over 0.5μm in diameter, more preferably over 1.0μm and most preferably over 2μm in diameter.

Preferably the microspheres are prepared from a bio-compatible material that will get in contact with the mucosal surface. Substantially uniform solid microspheres are preferred. Starch microspheres (crosslinked if necessary) are a preferred material. Other materials that can be used to form microspheres include gelatin, albumin, collagen, dextran and dextran derivatives. Preparation of these microspheres is well described in the pharmaceutical literature (see for example Davis et al., (Eds), "Microsphere and Drug Therapy", Elsevier Biomedical Press, 1984). Emulsion and phase separation methods are both suitable. For example, albumin microspheres may be made using the water-in-oil emulsification method where a dispersion of albumin is produced in a suitable oil by homogenization techniques or stirring techniques, with the addition if necessary of

small amounts of an appropriate surface active agent. The size of the microspheres is largely dictated by the speed of stirring or homogenization conditions. The agitation can be provided by a simple laboratory stirrer or by more sophisticated devices such as a microfluidizer or homogenizer. Emulsification techniques are also used to produce starch microspheres as described in GB 1 518 121 and EP 223 303 as well as for the preparation of microspheres of gelatin. Proteinaceous microspheres may also be prepared by coacervation methods such as simple or complex coacervation or by phase separation techniques using an appropriate solvent or electrolyte solution. Full details of the methods of preparing these systems can be obtained from standard text books (see for example Florence and Attwood, Physicochemical Principles of Pharmacy 2nd Ed.. MacMillan Press, 1988 Chapter 8.

The microspheres obtained may be sieved if necessary in order to separate out microspheres in the desired size range. Other size separation techniques (air elutriation) could also be employed. The final microspheres can be modified by chemical cross-linking or heat treatment. The active agent can be incorporated into the microspheres during their formulation or sorbed into/onto the system after preparation. The effectiveness of the system can be controlled by the physical nature of the microsphere matrix and, for example, the extent of cross linking. The

microsphere delivery systems may also include microspheres made from the active peptide or protein itself such as insulin microspheres.

As an added advantage the particles may have variable controlled release characteristics through modifications made to the microsphere system, for example by controlling the degree of cross-linking or by the incorporation of excipients that alter the diffusional properties of the administered drug. The amount of drug that can be carried by the microspheres is termed the loading capacity, which is determined by the physico-chemical properties of the drug molecule and in particular its size and affinity for the particle matrix. Higher loading capacities are to be expected when the administered drug is incorporated into the microspheres during the actual process of microsphere manufacture. It is known that for many peptides and proteins the amount of drug substance to be administered for a resultant therapeutic effect will be of the order of a few micrograms or less. Microcapsules of a similar size, which are bioadhesive and which have controlled release properties, would also be expected to provide similar benefit in terms of an increased and modified bio-availability of administered drugs. These microcapsules can be produced by a variety of methods. The surface of the capsule could be adhesive in its own right or could

be modified by coating methods familiar to those skilled in the art. These coating materials are preferably bioadhesive polymers such as polycarbophil, carbopol, DEAE-dextran or alginates. These microcapsules are deemed to be "microspheres" for the purposes of this specification and, again, more than 0.1μm in diameter but less than 10μm.

Using the combination of microspheres and drug, it has been found that the bioadhesive microsphere systems have the ability to enhance greatly the bioavailability of drugs, especially polar drugs, when they are administered together.

This potentiation of effect is believed to be due to the greater retention of the delivery systems in the nasal cavity.

The microsphere composition can also afford protection of the drug against degradation by enzymes.

The drug delivery system of the invention may advantageous-ly comprise an absorption enhancer. By "enhancer", we mean any material which acts to increase absorption across the mucosa. Such materials include mucolytic agents, degradative enzyme inhibitors and compounds which increase permeability of the mucosal cell

membranes. Whether a given compound is an "enhancer" can be determined by comparing two formulations comprising a non-associated, small polar molecule as the drug, with or without the enhancer, in an _in vivo_ or good model test and determining whether the uptake of the drug is enhanced to a clinically significant degree. The enhancer should not produce any problems in terms of chronic toxicity because _in vivo_ the enhancer should be non-irritant and/or rapidly metabolised to a normal cell constituent that does not have any significant irritant effect.

A preferred enhancing material is the material lysophosphatidylcholine obtainable from egg or soy lecithin. Other lysophosphatidylcholines that have different acyl groups as well as lyso compounds produced from phosphatidylethanolamines and phosphatidic acid which have similar membrane modifying properties may be used. Acyl carnitines (e.g. palmitoyl-dl carnitine-chloride) is an alternative. A suitable concentration is from 0.02 to 10%.

Other enhancing agents that are appropriate include chelating agents (EGTA, EDTA, alginates), surface active agents (especially non-ionic materials), acyl glycerols, fatty acids and salts, tyloxapol and biological detergents listed in the SIGMA Catalog, 1988, page 316-

321. Also agents that modify the membrane fluidity and permeability are appropriate such as enamines (e.g. phenylalanine enamine of ethyl-acetoacetate), malonates (e.g. diethyleneoxymethylene malonate), salicylates, bile salts and analogues and fusidates. Suitable concentrations are up to 10%.

The same concept of delivery of a drug incorporated into or onto a bioadhesive microsphere with an added pharmaceutical adjuvant applies to systems that contain active drug and mucolytic agent, peptidase inhibitors or non-drug polypeptide substrate singly or in combination. Suitably mucolytic agents are thiol-containing compounds such as N-acetylcysteine and derivatives thereof. Peptide inhibitors include actinonin, amastatin, Bestatin, Chloroacetyl-HOLeu-Ala-Gly-NH_2, diprotin A and B, ebelactone A and B, E-64, leupeptin, pepstatin A, phisphoramidon, H-Thr-(tBu)-Phe-Pro-OH, aprotinin, kallikrein, chymostatin, benzamidine, chymotrypsin, trypsin. Suitable concentrations are from 0.01 to 5%. The man skilled in the art will readily be able to determine whether an enhancer should be included.

The microsphere composition may be used with drugs selected from the following non-exclusive list: insulin, calcitonins (for example porcine, human, salmon, chicken, or eel) and synthetic modifications thereof*,

Interferons.

The starred drugs are especially preferred for administration with the microsphere system of the invention.

Further drugs include: antibiotics and antimicrobial agents such as tetracyline hydrochloride, leucomycin, penicillin, penicillin derivatives, erythromycin, sulphathiazole and nitrofurazone; local anaesthetics such as benzocaine; vasoconstrictors such as phenylephrine hydrochloride, tetrahydrozoline hydrochloride, naphazoline nitrate, oxymetazoline hydrochloride and tramazoline hydrochloride; cardiotonics such as digitalis and digoxin; vasodilators such as nitroglycerine and papaverine hydrochloride; antiseptics such as chlorhexidine hydrochloride, hexylresorcinol, dequaliniumchloride and ethacridine; enzymes such as

lysozyme chloride, dextranase; bone metabolism controlling agents such as vitamin D, and active vitamin D_3; Vitamin C;

Sex hormones; hypotensives; sedatives; anti-tumour agents; steroidal anti-inflammatory agents such as hydrocortisone, prednisone, fluticasone, prednisolone, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, beclomethasone, and beclomethasone dipropionate; non-steroidal anti-inflammatory agents such as acetaminophen, aspirin, aminopyrine, phenylbutazone, medanamic acid, ibuprofen, diclofenac sodium, indomethacine, colchicine, and probenocid; enzymatic anti-inflammatory agents such as chymotrypsin and bromelain seratiopeptidase; anti-histaminic agents such as diphenhydramine hydrochloride, chloropheniramine maleate and clemastine; anti-allergic agents and antitussive-expectorant antasthmatic agents such as sodium chromoglycate, codeine phosphate, and isoproterenol hydrochloride.

The molecular weight of the drug is preferably in the range 100 to 300,000.

In order to improve the properties, appearance or odour of the pharmaceutical composition, it may, if desired, contain any of known additives such as coloring

agents, preservatives, antiseptics, etc. Examples of colouring agents, include β-carotene, Red No. 2 and Blue No. 1; examples of preservatives include stearic acid, ascorbyl stearate and ascorbic acid; examples of antiseptics, include p-hydroxy-benzoate, phenol, chlorobutanol, etc.; and examples of corrigents include menthol and citrus perfume.

A further embodiment of the invention provides a kit comprising a drug delivery composition and means to deliver the composition to the nasal mucosa in a gas stream. The gas stream may be air or any other physiologically harmless gas. Preferably the means is such that, in use, the product of the flow rate and the square of the microsphere diameter is greater than 2000 μm^2 lit/min.

The deposition in the nose will depend on two factors: the size of the particles (aerodynamic diameter da) and flow rate (F) of inspiratory air.

The controlling factor is da^2F where da is measured in microns and F in lit/min.

The product da^2F should exceed 2000 to give the required deposition in the nasal cavity of the total dose. Resting ventilation is of the order of 30 lit/min.

Under extreme exertion or rapid inhalation, a very large fraction of the deposition takes place within the anterior non-ciliated part of the nose, where particles are retained for long time periods gradually being dragged along to the nasopharynz by the mucus drag effect. Details of deposition and flow rate studies may be found in the art, for example G.M. Hidy, Aerosols, Academic Press Inc. 1984.

For particulate systems administered to the respiratory tract, it is necessary to consider the aerodynamic diameter that takes into account the size of the particle and its density. For example, a particle with a physical diameter of 0.5 µm and density of 10 will behave like a larger particle (of greater than 2 microns) of unit density. This applies strictly to spherical particles and may be varied markedly by the shape of the particle. The aerodynamic (kinetic diameter) has been defined as the diameter of a hypothetical sphere of unit density having the same terminal setting velocity as a particle in question regardless of its geometric size, shape and true density.

The microspheres, in for example a freeze dried form, can be administered to the nasal cavity using a nasal insufflator device or pressurised aerosol cannister. Examples of these are already employed for

been found to be easier to administer using devices, especially those working on the basis of pressure packs and accurate valves and actuators as fewer problems with blockages occur.

Small microspheres are also easier to fluidize in powder administration devices, such as insufflators.

The narrower size range has been found to give a more uniform dose for an active material such as a peptide. The narrower size range has also been found to minimize separation of large and small particles on storage and transport and during administration. The admixture of insulin and microcrystalline cellulose as described in the prior art such as EP 122 036 results in a system that can undergo separation of particles on storage, shipment and administration. For example, when evaluated using an Andersen Impactor, the insulin was found largely in the smaller size fractions and the cellulose in the larger fractions. This could lead to

non-uniformity of dosing and unpredictive absorption. Greater control over the deposition site in the nose can be achieved with smaller and more uniform particles.

The main advantage found with the small bioadhesive microspheres of the present invention is that the increased surface area to volume ratio increases the carrier capacity when the drug is adsorbed onto and into the microspheres. Thus the small microspheres can carry more drug and minimize the amount of carrier used.

EXAMPLE 1

Production of albumin microspheres

Albumin microspheres were produced by a modification of the method described by Ratcliffe et al (1984). One ml of different concentrations (5%) of human serum albumin or ovalbumin at pH 6.8 was added to 25 ml of olive oil or light mineral oil with or without 0.25 ml of Span 85. The mixture was stirred in a mix-cell for 10 min, under turbulent flow conditions to form a w/o emulsion, using a mechanical stirrer (Heidolph) at 775 rpm (Tachometer DOT 1, Compact Instruments). Glutaraldehyde solution 25% (w/v) was added to 3.6% (v/v) of aqueous phase and the emulsion stirred for a further 30 min to denature and cross-link the albumin. The microspheres were collected by centrifugation at 2500 g for 20 min. The oil was then

removed and the spheres washed with diethyl ether followed by ethanol. The microspheres were collected by decantation.

EXAMPLE 2

The preparation of spherical particles of starch

5 g potato starch were dissolved in 95 ml of water at about 90°C. A second solution was prepared from 3 g of polyethylene glycol (m_w=6000) and 47 ml of water. This solution was heated to about 70°C, whereafter the warm starch solution was added while stirring, to form an emulsion. When the two-phase system had formed (with the starch solution as the inner phase) the mixture was allowed to cool to room temperature under continued stirring, wherewith the inner phase was converted to gel particles. The particles were filtered off at room temperature and stirred in 100 ml of ethanol, whereafter the particles were again filtered off and laid to dry in air.

The yield was 90%.

CLAIMS

1. A drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and active drug associated with each microsphere, at least 90 wt % of the microspheres having a diameter of 0.1 μm or more but less than 10 μm.

2. A drug delivery composition according to Claim 1 wherein the microspheres are adapted to gel in contact with the mucosal surface.

3. A drug delivery composition according to Claim 1 or Claim 2 wherein the microspheres comprise starch, starch derivatives, gelatin, albumin, collagen, dextran or dextran derivatives.

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 3 or Claim 4 wherein the microsphere material is at least partially cross-linked.

6. A drug delivery composition according to Claim 1 or Claim 2 wherein the microspheres are formed from the active drug itself.

8. A drug delivery composition according to

wherein the absorption enhancer is a surfactant, a lysophosphatidyl-choline such as lysolecithin or a lysophosphatidylglycerol.

9. A drug delivery composition according to any one of the preceding claims wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A kit comprising a drug delivery composition according to any one of the preceding claims and means to deliver the composition to the nasal mucosa in a gas stream.

12. A kit according to Claim 11 wherein the means is such that, in use, the produce of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2 lit/min.